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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
50-783

Pharmacology Review(s)

NDA 50-783

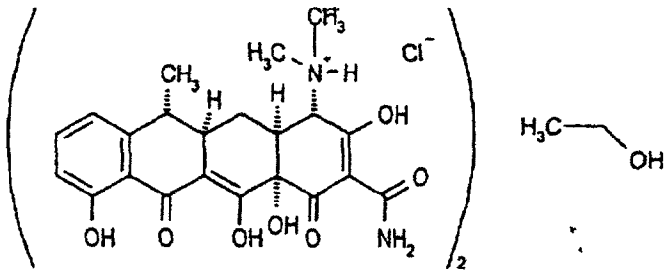
SEP 25 2000 (Per CDFs)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: Doxycycline; periodontitis
Reviewer Name: Norman A. See, Ph.D.
Division Name: DDDDP; HFD-540
Review completion Date: 18-SEP-2000
Review number: 001
IND/NDA number: NDA 50-783
Serial number of submission: 000
Letter date of submission: 31-MAR-2000
Center receipt date: 03-APR-2000
Information to sponsor: Yes ( ) No (X)
Sponsor (or agent): Collagenex Pharmaceuticals, Inc.

Drug:

Code name: None
Generic name: Doxycycline Hyclate, USP
Trade name: Periostat tablets
Chemical name: 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride
CAS registry number: 17086-28-1
Molecular formula/Molecular weight: $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$/1025.89
Structure:



Relevant INDs/NDAs/DMFs: IND [redacted] NDA 50-744

Drug class: Antibiotic. However, it is used as a collagenase inhibitor at a sub-antimicrobial level in connection with this application.

Indication: Treatment of periodontitis

Clinical formulation: Tablets that contain:

	mg per Tablet
Doxycycline hyclate, USP	23.00*
Microcrystalline cellulose, NF	[redacted]
Magnesium stearate, NF	

*Equivalent to 20.0mg doxycycline

Route of administration: Oral

Proposed clinical protocol or use: Two tablets per day (40mg doxycycline per day, or 0.67mg/kg/day in a 60kg individual; expressed as the salt, the dosage is 46mg doxycycline hyclate per day, or 0.77mg/kg/day). The product is

labeled for up to nine months of continuous use per treatment episode. The maximum number of treatment episodes that a given patient may undergo is unclear, but is unlikely to be more than three or four (according to the clinical reviewer).

Previous clinical experience: Please see the original pharmacology summary of NDA 50-744.

Background and product history: An essentially identical product, Periostat capsules, was approved under NDA 50-744. The sponsor wishes to be able to market a tablet formulation of Periostat, and NDA 50-783 was submitted to that end. The formulations and proposed usage of the two products are identical, with the exception that the tablets contain ( )(a film coating agent) in lieu of a hard gelatin capsule.

Studies reviewed within this submission: None. Please see the Pharmacology reviews of NDA 50-744 for evaluation of applicable data.

Studies not reviewed within this submission: None.

OVERALL SUMMARY AND EVALUATION:

Safety Evaluation: The proposed exposure to doxycycline is identical to that approved under NDA 50-744; please see the Pharmacology reviews of NDA 50-744 for evaluation of applicable data. The only difference between the tablet and capsule formulations is that the tablets contain( )(a film coating agent) in lieu of a hard gelatin capsule. The formulation of ( )is:

Ingredient	Amount (%, w/w)

The daily exposure to these compounds resulting from use of Periostat tablets (two tablets per day, or a total of) would be:

Ingredient	Daily Exposure (mg)

All of the components of ( )are listed in the CDER Inactive Ingredient Guide as having been excipients in drug products that were approved for oral use, as are other formulations of ( ). ( )is a component of many foods, including dairy products. ( )is GRAS as a direct food additive (21 CFR 172.874). ( )is listed as a diluent in color additive mixtures for drug use (21 CFR 73.1575). ( )is GRAS as a direct food additive (21 CFR 184.1901 and 21 CFR 582.1901). These exposures are acceptable.

Clinical relevance of safety issues: None
Other clinically relevant issues: None
Conclusions: The proposed exposure to the drug product is safe.
Communication review:
- Labeling review (NDA):

Labeling: The submitted draft label, which duplicates the currently approved label for Periostat capsules with respect to the warnings, pregnancy category and carcinogenesis sections, is acceptable to this reviewer.

RECOMMENDATIONS:

Internal comments: NDA 50-783 is approvable in regard to pharmacologic and toxicologic concerns.
External Recommendations (to sponsor): None
Draft letter Content for Sponsor: None
Future development or NDA issues: The sponsor has committed (under NDA 50-744) to conduct a two-year carcinogenesis bioassay with doxycycline hyclate in rats, and to submit the data when they become available. The most recent annual report submitted to NDA 50-783 indicated that the in-life phase of the bioassay had been completed and the report is in preparation. When those data are submitted and reviewed, the labels of NDA 50-744 and NDA 50-783 will be updated.

APPEARS THIS WAY
ON ORIGINAL

Table 6

Summary of Bioavailability (BA) Results: Statistics for Pharmacokinetic Parameters by Treatment and Gender

Parameter	Treatment	Statistic	Per Protocol			Intent-to-Treat		
			Males	Females	Total	Males	Females	Total
AUC 0-inf								
	F	N	9	10	19	9	10	19
		Arithmetic Mean	4883	5557	5238	4883	5557	5238
		Geometric Mean	4568	5359	4969	4568	5359	4969
		Coefficient of Variation (%)	41.5	29.7	34.7	41.5	29.7	34.7
	T	N	9	10	19	9	11	20
		Arithmetic Mean	5671	5984	5836	5671	5949	5824
		Geometric Mean	5259	5700	5487	5259	5691	5493
		Coefficient of Variation (%)	45.6	32.7	38.0	45.6	31.2	37.1
AUC 0-t								
	F	N	9	10	19	9	10	19
		Arithmetic Mean	4055	4392	4232	4055	4392	4232
		Geometric Mean	3713	4286	4004	3713	4286	4004
		Coefficient of Variation (%)	46.1	23.5	34.4	46.1	23.5	34.4
	T	N	9	10	19	9	11	20
		Arithmetic Mean	5069	5089	5079	5069	5091	5081
		Geometric Mean	4616	4748	4685	4616	4780	4706
		Coefficient of Variation (%)	50.3	38.3	43.0	50.3	36.3	41.9
Cmax								
	F	N	9	10	19	9	10	19
		Arithmetic Mean	243.6	297.2	271.8	243.6	297.2	271.8
		Geometric Mean	225.8	292.6	258.8	225.8	292.6	258.8
		Coefficient of Variation (%)	42.5	19.0	31.1	42.5	19.0	31.1
	T	N	9	10	19	9	11	20
		Arithmetic Mean	308.3	410.0	361.8	308.3	417.2	368.2
		Geometric Mean	294.1	403.2	347.2	294.1	410.4	353.2
		Coefficient of Variation (%)	33.8	18.0	28.0	33.8	17.7	27.9
tmax								
	F	N	9	10	19	9	10	19
		Arithmetic Mean	3.22	3.55	3.39	3.22	3.55	3.39
		Geometric Mean	2.70	3.33	3.01	2.70	3.33	3.01
		Coefficient of Variation (%)	65.9	35.4	49.5	65.9	35.4	49.5
	T	N	9	10	19	9	11	20
		Arithmetic Mean	1.33	1.45	1.39	1.33	1.41	1.38
		Geometric Mean	1.27	1.39	1.33	1.27	1.35	1.31
		Coefficient of Variation (%)	37.5	30.2	32.9	37.5	31.0	33.1

Table 6

Summary of Bioavailability (BA) Results: Statistics for Pharmacokinetic Parameters by Treatment and Gender

Parameter	Treatment	Statistic	Per Protocol			Intent-to-Treat		
			Males	Females	Total	Males	Females	Total
t 1/2								
	F	N	9	10	19	9	10	19
		Arithmetic Mean	21.38	19.37	20.32	21.38	19.37	20.32
		Geometric Mean	20.71	18.25	19.38	20.71	18.25	19.38
		Coefficient of Variation (%)	26.1	38.3	32.0	26.1	38.3	32.0
	T	N	9	10	19	9	11	20
		Arithmetic Mean	18.70	17.48	18.06	18.70	17.20	17.88
		Geometric Mean	18.18	16.81	17.44	18.18	16.57	17.28
		Coefficient of Variation (%)	25.2	29.5	26.9	25.2	28.9	26.8
lambda_z								
	F	N	9	10	19	9	10	19
		Arithmetic Mean	0.0346	0.0401	0.0375	0.0346	0.0401	0.0375
		Geometric Mean	0.0335	0.0380	0.0358	0.0335	0.0380	0.0358
		Coefficient of Variation (%)	27.2	32.4	30.6	27.2	32.4	30.6
	T	N	9	10	19	9	11	20
		Arithmetic Mean	0.0392	0.0429	0.0412	0.0392	0.0434	0.0415
		Geometric Mean	0.0381	0.0412	0.0397	0.0381	0.0418	0.0401
		Coefficient of Variation (%)	25.2	28.9	27.1	25.2	27.4	26.4

5. DISCUSSION AND CONCLUSIONS

The objectives of this study were to test for bioequivalence between the currently-marketed doxycycline hyclate 20 mg capsule and a doxycycline hyclate 20 mg tablet; and to evaluate possible food effects in the pharmacokinetic profile of doxycycline hyclate 20 mg tablets.

The capsule and tablet formulations of doxycycline are bioequivalent since the 90% confidence interval for the ratio of means for both AUC and C_{max} fell within 80%-125%. The least squares mean was close to 100%, which indicates a high level of bioequivalence.

AUC and C_{max} were higher, and $t_{1/2}$ was shorter in females than males. These gender differences appear to be more marked for the fasted capsule condition compared to the fasted tablet condition as summarized in the following Table 7:

Table 7: Summary of Gender Analysis

Study	Entity	Parameter	Male (M)	Female (F)	Comments
Bioequivalence	Fasted Capsule	$AUC_{0-\infty}$	4925 ng.h/mL	6025 ng.h/mL	F22.3%>M
	Fasted Tablet	$AUC_{0-\infty}$	5259 ng.h/mL	5700 ng.h/mL	F8.4%>M
	Fasted Capsule	C_{max}	243.6 ng/mL	418.1 ng/mL	F71.6%>M
	Fasted Tablet	C_{max}	294.1 ng/mL	403.2 ng/mL	F37.1%>M
	Fasted Capsule	$t_{1/2}$	22.0 hr	16.7 hr	M31.7%>F
	Fasted Tablet	$t_{1/2}$	18.7 hr	17.5 hr	M6.9%>F
Bioavailability (Food Effect)	Fed Tablet	$AUC_{0-\infty}$	4568 ng.h/mL	5359 ng.h/mL	F17.3%>M
	Fasted Tablet	$AUC_{0-\infty}$	5259 ng.h/mL	5700 ng.h/mL	F8.4%>M
	Fed Tablet	C_{max}	225.8 ng/mL	292.6 ng/mL	F29.6%>M
	Fasted Tablet	C_{max}	294.1 ng/mL	403.2 ng/mL	F37.1%>M
	Fed Tablet	$t_{1/2}$	21.4 hr	19.4 hr	M10.3%>F
	Fasted Tablet	$t_{1/2}$	18.7 hr	17.5 hr	M6.9%>F
	Fed Tablet	t_{max}	3.22 hr	3.55 hr	F10.3%>M
	Fasted Tablet	t_{max}	1.33 hr	1.45 hr	F9.0%>M

There is a food effect since the 90% lower confidence limit for the ratio of means (fed to fasted) for AUC fell below 80% and the 90% lower confidence limit for the ratio of means (fed to fasted) for C_{max} fell below 70%. The AUC and C_{max} were lower and the t_{max} was higher in the fed state, indicating that food decreases the rate and extent of absorption and delays the time at which maximal concentrations are reached.

Female subjects had a higher AUC and maximum concentration (C_{max}), a longer t_{max}, and a shorter $t_{1/2}$ than males. Gender differences in AUC and $t_{1/2}$ appear to be more marked for the fed tablet condition compared to the fasted tablet condition. Conversely, for C_{max},

a more marked gender difference is seen in the fasted tablet condition compared to the fed tablet condition (Table 7).

Final Conclusions

The capsule and tablet formulations of doxycycline are bioequivalent since the 90% confidence interval for the ratio of means for both AUC and C_{max} fell within 80%-125%. There is a food effect since the 90% lower confidence limit for the ratio of means (fed to fasted) for AUC fell below 80% and the 90% lower confidence limit for the ratio of means (fed to fasted) for C_{max} fell below 70%. Food decreases the rate and extent of absorption and delays the time at which maximal concentrations are reached.

6. COMMENTS:

- The sponsor discussed differences in pharmacokinetic parameters between males and females in several places. However, in their demographic distribution table, they did not report individual or mean weight of the male and female patients. Given that mean female weight is 1/3rd less than mean male weight, a weight normalized analysis of the individual pharamcoknietics parameters could have eliminated the observed differences in pharmacokinetic parameters between male and female subpopulation and rendered the following comments redundant.

- In both bioequivalence and food effect bioavailability studies, it was found that AUC and C_{max} were higher, and $t_{1/2}$ was shorter in females than males. It is an apparent anomaly to the conventional relationship between AUC and $t_{1/2}$ which should be proportional to each other.

- Though AUC and Cmax were higher in females than males, the extent of the difference does not call for recommendation for any dose adjustment.

- Comments pertaining to gender differences in the subheading *Gender* under **Clinical Pharmacology** labeling should be eliminated.

7. LABELING COMMENTS:

Following modifications have been proposed in the "**Clinical Pharmacology**" section of the labeling. "~~Strikeout~~" means suggested deletions and "Shading" suggests insertion of new text.

Pharmacokinetics

The pharmacokinetics of doxycycline following oral administration of Periostat® were investigated in 4 volunteer studies involving 107 adults. Additionally, doxycycline pharmacokinetics have been characterized in numerous scientific publications.[2] Pharmacokinetic parameters for Periostat® following single oral doses and at steady-state in healthy subjects are presented as follows:

DRAFT

Gender

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/s/

Tapash Ghosh
1/16/01 12:16:40 PM
BIOPHARMACEUTICS

Dennis Bashaw
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BIOPHARMACEUTICS